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COVID-19 Precautionary Measures and Type 1 Diabetes Patients in Saudi Arabia



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ABSTRACT

Aim: To minimize the spread of COVID-19, the Kingdom of Saudi Arabia (KSA) enforced a nationwide lockdown. We aimed to explore whether the manner in which Saudi patients with type 1 diabetes (T1D) manage their disease has changed during this unparalleled lockdown.

Methods: An online survey exploring the effect of lockdown on T1D outcomes was distributed among T1D patients residing in KSA during lockdown.

Results: A total of 1010 patients responded to the survey. Around 40% reported communicating with their physicians during lockdown. Age, level of education, residence, previous visits to diabetes education clinics, last HbA1c value, and average monthly income were all significantly associated with communication with the treating physician ($p = 0.008$, $p < 0.001$, $p < 0.001$, $p = 0.002$, $p < 0.001$, and $p < 0.001$, respectively). Age, level of education, and average monthly income were significantly associated with experiencing severe hypoglycemia ($p = 0.036$, $p = 0.03$, and $p < 0.001$, respectively), while average monthly income and level of education were significantly associated with experiencing diabetic ketoacidosis (DKA) ($p < 0.001$ and $p = 0.0039$, respectively); during lockdown. Patients who communicated with their physicians reported lower rates of severe hypoglycemia compared to those who did not (25.2% vs 30.7%, respectively).

Conclusion: Age and level of education were significantly associated with communication with the treating physician, and experiencing severe hypoglycemia and DKA; in patients with T1D during the lockdown period in Saudi Arabia. Keeping two-way virtual communication channels between physicians and their T1D patients should be encouraged.

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1. Introduction

Much of the global concern at present is focused on coronavirus disease-19 (COVID-19), the highly infectious respiratory disease which originated in Wuhan, China [1]. From a small cluster of Chinese cases of pneumonia with unknown cause to a global pandemic in a short span of time, it made sense that drastic measures were implemented to prevent the rapid spread of the disease; most of which were deemed necessary but very challenging. Among the mitigation strategies implemented by many countries were the closure of non-essential businesses and the implementation of stay-at-home orders. While most experts agree

that these draconian policies were justified, the full debilitating consequences of such policies can only be revealed once the pandemic is over. Among the more prominent collateral damages is the severe imbalance in the healthcare system. With its full force focused on COVID-19 patients, patients with other diseases, specifically chronic disorders such as type 1 diabetes (T1D), were left heavily ignored.

The Kingdom of Saudi Arabia (KSA), like most countries, has not been spared from COVID-19. In fact, in an effort to curb the spread of the still ongoing coronavirus pandemic, KSA imposed nationwide lockdowns and 24-h curfews in most of its regions [2]. This meant that outdoor activities, including visiting diabetes clinics and having face to face contact with endocrinologists were limited for most patients including patients with T1D [3]. In addition to that, the emotional burden of having to manage a complicated disease such as T1D, plus the continuous daily requirements of medication dosing, self-monitoring of blood glucose, physical activity, and a healthy diet are often linked to poorer glycemic control and less rigorous dietary patterns and physical exercise [4].

Hence, the effects of prolonged lockdown on the glycemic control of T1D patients in Saudi Arabia warrants investigation. In this study, we aimed to explore whether the manner in which Saudi T1D patients manage their disease has changed during lockdown.

2. Materials and methods

2.1. Design and subjects

In this cross-sectional study, conducted between April 26 and May 7, 2020, a nationwide online survey was cascaded to healthcare workers to distribute to their respective T1D patients. Patients with T1D were asked to distribute the survey to others with T1D through WhatsApp application. For the purpose of this study, only T1D patients residing in KSA during the study timeframe were eligible for inclusion. A total of 1010 patients filled the survey; all of whom provided informed consent prior to filling the survey. Respondents' anonymity and confidentiality of information provided were assured. Ethical approval was obtained from the Institutional Review Board (IRB) of King Khalid University Hospital, Riyadh, KSA.

2.2. Survey

An Arabic survey composed of four sections was developed. The sections were: demographics, insulin and blood glucose monitoring, complications, and the effects of lockdown on T1D outcomes. The survey was reviewed by three endocrinologists, three patients with T1D, one endocrine fellow, and three healthcare workers (DM educators and a dietician) for content validity. The final version was created on google forms and circulated via WhatsApp. The survey is included as a Supplementary file.

2.3. Statistical analysis

All tests were performed with 5% level of significance. Missing data were not counted in the percentages. Data were analyzed using SPSS software version 25, IBM, USA. Quantitative variables are presented as mean and standard deviation (SD) and categorical variables are presented as frequencies and percentages (%). Chi² test was used to measure association between unpaired categorical variables. Fisher's exact test was used when the assumptions of Chi² test were unmet.

3. Results

3.1. Patients' characteristics

Data were collected from a total of 1010 (100%) T1D patients. The survey was answered by the parents of 514 patients with T1D (50.9%) while 496 patients (49.1%) answered the survey by themselves. About 39% of patients (n = 397) were from the central region. More than half of the patients (n = 587, 58.1%) held a degree beyond high school. The predominant age group in our population was that between 14 and 40 years of age (n = 572, 56.6%) followed by those less than 14 years (n = 318, 31.5%). During the 12 months preceding COVID-19 pandemic, 177 patients (17.5%) experienced DKA (of whom 141 (80.6%) were admitted to the ER, the ward, or the ICU as a result) and 35.8% of the patients reported severe hypoglycemia that necessitated external help. More details about patients' characteristics are shown in [Table 1](#).

3.2. Patients' demographics and T1D outcome

We assessed the association between patients' demographics and the occurrence of severe hypoglycemia and DKA. Age, level of education, and monthly income were significantly associated with experiencing severe hypoglycemia (p = 0.036, p = 0.03, and p < 0.001, respectively); while monthly income and level of education were significantly associated with reporting DKA (p < 0.001 and p = 0.0039, respectively). Among the different age groups explored, patients aged less than 14 years were the highest to report severe hypoglycemia (33%). Among different educational levels, patients with Master's or PhD degree were the least to report severe hypoglycemia (14.5%) while none of them experienced DKA. Lastly, among different subcategories of monthly income, patients with an average monthly income exceeding 20K were the least to report severe hypoglycemia (16.7%) and the least to experience DKA (3.9%).

3.3. Management of T1D patients during lockdown

The frequency of BG monitoring since the 6th of March 2020 was not affected in most of the patients (n = 696, 69.8%). In addition, 404 (40.0%) had contact with their physician to follow-up on their diabetes during lockdown. A total of 406 patients (40.2%) faced some difficulties in getting insulin, glucose testing strips, FreeStyle Libre[®], ketone testing strips, or pump supplies during lockdown. These difficulties were mainly the lack of a delivery option from the clinic (31.8%), delay from the delivering company (22.9%), lack of communication with the clinic (34.2%), lack of a delivery option for diabetes supplies from the hospital (31.3%), and delivery of incorrect medications (16.5%). A slightly higher proportion (n = 441, 43.7%) had to pay for these supplies with their own money.

Having a monthly income exceeding 20K SAR was significantly associated with reduced frequency of facing difficulty in getting the required supplies (26.8%, p < 0.001). Moreover, reporting difficulty in getting insulin, glucose testing strips, FreeStyle Libre[®], ketone testing strips, or pump supplies was significantly associated with severe hypoglycemia (Odds Ratio [OR] = 1.94; 95% confidence interval [CI], 1.47–2.56, p < 0.001), having to switch from insulin pump to insulin injections (OR = 20.6; 95% CI, 2.58–164.37, p < 0.001), and self-payment for these supplies (OR = 3.86; 95% CI, 2.96–5.04, p < 0.001).

A total of 60 patients (5.9%) and 288 patients (28.5%) reported DKA and severe hypoglycemia during lockdown, respectively. Among those who reported DKA, 83.6% did not think that measures taken by the health authority or the curfew instigated their DKA. More details are provided in [Table 2](#).

Table 1
Sociodemographic characteristics of the population & management of T1D pre-lockdown (N = 1010).

Characteristics	Count (%)		
Age groups	Less than 14 years	318 (31.5)	
	From 14 to 20 years	200 (19.8)	
	From 21 to 30 years	234 (23.2)	
	From 31 to 40 years	138 (13.7)	
	From 41 to 50 years	73 (7.2)	
	More than 50 years	47 (4.7)	
Residency in Saudi Arabia	Central region	397 (39.3)	
	Western region	322 (31.9)	
	Eastern region	107 (10.6)	
	Northern region	107 (10.6)	
Level of education	Southern region	77 (7.6)	
	Secondary school or less	423 (41.9)	
	Diploma	75 (7.4)	
	Bachelor's degree	443 (43.9)	
Average family monthly income (SAR)	Master's or PhD degree	69 (6.8)	
	Less than 5K	234 (23.2)	
	5K–10K	307 (30.4)	
	11K–15K	204 (20.2)	
Type of hospital visited for follow-ups	16K–20K	127 (12.6)	
	More than 20K	138 (13.7)	
	Government hospital	875 (86.6)	
Type of clinic visited for follow-ups	Private hospital	135 (13.4)	
	Endocrine & diabetes clinic	872 (86.3)	
Form of insulin used	Family medicine & community clinic	44 (4.4)	
	Insulin pump	214 (21.2)	
	Insulin syringes	47 (4.7)	
	Insulin pen	749 (74.2)	
Type of BG monitors used	Internal medicine clinic	71 (7.0)	
	Primary care clinic	23 (2.3)	
	Patient monitors BG	985 (97.5)	
	Finger-prick glucometer	466 (47.3)	
Last HbA1c value (n = 904) ^a	FreeStyle Libre®	445 (45.2)	
	Medtronic CGM paired with pump	50 (5.1)	
	CGM, Dexcom	24 (2.4)	
	7.0% or less (53 mmol/mol or less)	181 (20.0)	
Diabetic complications	7.1%–8.0% (54–64 mmol/mol)	266 (29.4)	
	8.1%–9.0% (65–75 mmol/mol)	219 (24.2)	
	More than 9.0% (>75 mmol/mol)	238 (26.3)	
		% of Responses	% of Cases
	Retinopathy	45.5	66.0
Neuropathy	29.2	42.4	
Nephropathy	9.6	13.9	
Cardiac complications	5.7	8.3	
Foot or vascular complications	10.0	14.6	

^a 106 patients did not know their last HbA1c value.

3.4. Factors associated with communication between T1D patients and their physicians during lockdown

Compared to those less than 14 years old or more than 40 years old, patients between 14 and 40 years were significantly more likely to report having communication with their physician during lockdown (p = 0.008). More specifically, the highest frequency (47%) of reporting communication with physicians was in patients aged between 21 and 30 years. Level of education was significantly associated with the likelihood of communicating with the treating physician (p < 0.001); 65.2% of patients with a Master's or PhD degree, 44% of patients with a Bachelor's degree, and 37.3% of patients with a diploma degree reported having communication with their physician during lockdown. Patients' residence as

Table 2
The Impact of the COVID-19 outbreak, precautionary measures, and lockdown on people with T1D in KSA.

Survey questions & responses (N = 1010)	n (%)
Have the health measures taken, including the applied curfew, during the COVID-19 period in KSA affected your frequency of testing your blood glucose? (n = 997)	
No, it did not	696 (69.8)
Yes, I test more than usual	204 (20.5)
Yes, I test less than usual	97 (9.7)
Have you communicated with your physician taking care of your diabetes during the COVID-19 period?	
Yes	404 (40.0)
No	606 (60.0)
Did you face difficulty in getting insulin, glucose testing strips, libre, ketone testing strips, or pump supplies during the COVID-19 period?*	
Yes	406 (40.2)
No delivery option from the clinic	129 (31.8)
Delay from the delivering company	93 (22.9)
No available communication with the clinic	139 (34.2)
No delivery option available for diabetes supplies from hospital	127 (31.3)
I received the delivery but not for the correct items needed	67 (16.5)
No	604 (59.8)
Did you have to pay out of your pocket for insulin, glucose testing strips, FreeStyle Libre®, ketone testing strips, or pump supplies during the COVID-19 period?	
Yes	441 (43.7)
No	569 (56.3)
Did you have to reduce your insulin doses or share other's insulin to avoid running out of insulin during the COVID-19 period?	
Yes	146 (14.5)
No	864 (85.5)
Have you experienced diabetic ketoacidosis during the COVID-19 period?	
Yes	60 (5.9)
Possibly due to limitation in communication with the physician (n = 56)	14 (25.0)
Possibly due to measures taken by the health authority or curfew (n = 55)	9 (16.4)
No	950 (94.1)
Have you suffered from severe hypoglycemia (requiring external help) during the COVID-19 period?	
Yes	288 (28.5)
Possibly due to limitation in communication with the physician (n = 275)	58 (21.1)
Possibly due to measures taken by the health authority or curfew (n = 271)	39 (14.4)
No	722 (71.5)
Did you benefit from the virtual communication with your physician (by phone, zoom, google duo or other social media applications)? (n = 444)	
Yes	398 (89.6)

* Patients were allowed to choose more than one answer.

well was a significant factor (p < 0.001); 50.6% of patients residing in the central region reported having communication with their physician compared to other regions (ranging from 22.4% to 37.7%). Patients who had previously visited diabetes education clinics were significantly more likely to report having communication with their physician than those who did not visit a diabetes education clinic before (42.5% vs 28.1%, p < 0.001). In addition, average family monthly income was also significantly associated with communicating with physicians; more patients with lower monthly income (71.4% of patients earning less than 5K) communicated with their physicians than those on the higher income range (45.7% of

Table 3
Factors affecting the level of communication between T1D patients and their physicians during lockdown.

Potential factors		Patients who reported communicating with their physicians during lockdown Count (%)	P value
Age groups	Less than 14 years	112 (35.2)	0.008
	From 14 to 20 years	83 (41.5)	
	From 21 to 30 years	111 (47.4)	
	From 31 to 40 years	61 (44.2)	
	From 41 to 50 years	26 (35.6)	
	More than 50 years	11 (23.4)	
Educational level	Secondary school or less	136 (32.2)	<0.001
	Diploma	28 (37.3)	
	Bachelor's Degree	195 (44.0)	
	Master's or PhD degree	45 (65.2)	
Average family monthly income (SAR)	Less than 5K	167 (71.4%)	<0.001
	5K–10K	184 (59.9%)	
	11K–15K	124 (60.8%)	
	16K–20K	68 (53.5%)	
	More than 20K	63 (45.7%)	
Residence	More than 20K	201 (50.6)	<0.001
	Eastern region	38 (35.5)	
	Northern region	24 (22.4)	
	Southern region	29 (37.7)	
	Western region	112 (34.8)	
Last HbA1c value	7.0% or less (53 mmol/mol or less)	90 (49.7)	0.002
	7.1%–8.0% (54–64 mmol/mol)	149 (56.0)	
	8.1%–9.0% (65–75 mmol/mol)	142 (64.8)	
	More than 9.0% (> 75 mmol/mol)	157 (66.0)	
	Have you ever visited a diabetes education clinic?		
Yes	354 (42.5)	<0.001	
No	50 (28.1)		

patients earning more than 20K). Last but not least, last recorded HbA1c value was also a significant factor; patients with poor glucose control reported the highest frequency of communication with their physicians (66%). More details are shown in [Table 3](#).

3.5. Effect of communication with the physician on the occurrence of severe hypoglycemia and DKA

Rate of severe hypoglycemia among patients who reported having communication with their physicians (25.2%) was lower than those who reported not having communication with their physicians (30.7%). Although this difference was not statistically significant at the 0.05 level, it was significant at a level of 0.1. On the other hand, the occurrence of DKA did not differ significantly ($p = 0.342$) between patients who communicated with their doctors and those who did not (5.0% vs 6.6%, respectively). More details are provided in [Table 4](#).

4. Discussion

In the present study, we aimed to explore the effects of the lockdown on the way T1D patients manage their disease in KSA. Additionally, we aimed to look for factors that could have affected the communication of T1D patients with their physicians, along with frequency of reporting indicators of inadequate glycemic control in these patients. This is to our knowledge the first survey across the kingdom to include such number of participants from all across the kingdom.

Most of the patients were living in either the central or western regions. Around half of our sample were 20 years old or younger and had T1D for more than 5 years. While most of the patients (~70%) continued their pre-pandemic frequency of blood glucose monitoring during the forced lockdown, we found that 26.3% reported an HbA1C value of more than 9.0% (75 mmol/mol) when last measured.

Since the value of HbA1C represents DM control of the patients prior the COVID-19 period, this indicates that a considerable proportion of T1D patients in this study had poor glycemic control pre-lockdown. Further investigation into the possible causes is necessary to find solutions to this issue.

We found that 14.5% of our patients had to reduce their insulin dose or share it with others to avoid running out of insulin. This proportion was less than that reported by Verma et al. in India; 26.9% of their patients missed insulin doses. In our study, 9.7% of the patients reported testing their blood glucose at a lower frequency during lockdown, while 38.5% reported not maintaining their blood glucose record in the study conducted by Verma et al. Similarly, 5.9% of the patients in our study reported having DKA compared to 7.7% in the Verma et al. study [5]. The most recent systemic review on the epidemiology of DKA in Arab patients with type 1 diabetes (conducted in 2016) showed that the frequency of DKA in KSA ranged from 25% to 80% of T1DM patients [6]. Given that our study relied mainly on self-reporting of DKA rather than a confirmatory laboratory diagnosis, and based on the fact that we conducted this study early in the lockdown period for only a short time window, it is expected that the DKA rate reported herein does not reflect the real rate during the COVID-19 period.

However, the rate of reporting severe hypoglycemia in our study (28.5%) was higher than that reported by Verma et al. In the latter, the rate of reporting hypoglycemic episodes was 15.3%, while the rate of hospitalization due to hypoglycemia was 1.9% [5].

Age, level of education, and monthly income were significantly associated with experiencing severe hypoglycemia. We observed that the younger age group (<14 years) had significantly higher chances of experiencing severe hypoglycemia and of not having communication with their treating physicians during the lockdown. The increased frequency of severe hypoglycemia in this age group is understandable given that young age is one of the non-modifiable predictors of severe hypoglycemia [7]. This could likely

Table 4
The effect of communication with the physician on the occurrence of hypoglycemia and diabetic ketoacidosis during the COVID-19 pandemic.

Potential factors	Did you communicate with your physician taking care of your diabetes during lockdown?	Yes	No	P-value*
		Count (%)	Count (%)	
Occurrence of severe hypoglycemia	Yes	102 (25.2)	186 (30.7)	0.060
	No	302 (74.8)	420 (69.3)	
Occurrence of DKA	Yes	20 (5.0)	40 (6.6)	0.342
	No	384 (95.0)	566 (93.4)	

* Using chi-square test at a level of significance = 0.05.

be attributed to the unpredictable activity and diet patterns of teenagers in general. This highlights the urgent need for more focus from healthcare workers on this age group.

We also noted that patients with post-graduate degrees were more likely to communicate with their physician and less likely to experience severe hypoglycemia or DKA. It should be noted that only 6.8% of our population belonged to this educational level while the majority (41.9%) attained secondary education or less; a fact which highlights the need for more attention directed to patients of secondary education or less. This should focus on the paramount value of reaching out for endocrinologists during the process of glucose self-control.

Furthermore, monthly income also had its share of association with T1D outcomes. We found that patients with a monthly income exceeding 20K (13.7% of our study population) were less likely to experience severe hypoglycemia and DKA and were also less likely to face difficulty in reaching their required supplies. This gives us impression that patients with a monthly salary on the high-end range were more aware on how to self-manage their T1D while evading severe hypoglycemia and DKA. Patients with limited income may be at disadvantage of not being able to attend diabetes education clinics or such service may not be provided in their area of residence. To facilitate healthcare equality in KSA, one of the proposed solutions is telecommunication with diabetes educators instead of physically attending DM education sessions. On a related note, having a monthly income of 8K or more was found to be a significant risk factor for developing diabetes and impaired fasting glucose (IFG) among children and adolescents in KSA [8]. We believe that these findings are of considerable importance as they demonstrate how the unpreparedness of healthcare systems may hugely affect vulnerable patients particularly those with low monthly income.

In our sample, 40.2% reported difficulties in getting insulin or diabetes-related supplies. These had significantly higher odds for reporting severe hypoglycemia, having to switch from insulin pump to insulin injections, and paying out of pocket for such supplies. Previous studies on the effect of natural disasters on diabetes management observed limited stock or unavailability of supplies during these times (6). Luckily, this was not the case in our study. Patients indicated that the lack of delivery options was the main reason behind the difficulty in getting their supplies. This an important point to be considered by healthcare planners in KSA in case of a further wave of COVID-19 or future pandemic.

Patients aged 14–40 years, those living in the central region, those holding a university degree or a post-graduate degree, those with the lowest monthly income (less than 5K), those with poor glucose control (>9.0% (>75 mmol/mol), and those who had visited a diabetes education clinic before; were all significantly more likely to have communicated with their physicians during lockdown. It is possible that patients with the lowest monthly income fear the financial consequences of poor glycemic control. Wilhems et al. reported that patients from lower social classes receive less participatory consultation and less medical information from their physicians [9]. Our finding that patients with the lowest monthly income reached out more to their physicians during lockdown

could be out of fear the financial consequences of poor glycemic control, and could also be due to an encouraging attitude from their physicians. In KSA, we lack studies examining the link between lower social class and healthcare access, which urges the need for large studies to examine the nature of the relationship between both.

It is expected that patients with the least HbA1c would take it upon themselves to reach out to their physicians during those desperate times; patients with controlled DM are managing their disease well, thus may not need to communicate with their physician as frequent as those with uncontrolled/poorly controlled DM.

Our study is the first to highlight the gap in northern and southern regions and address that work is needed to establish the infrastructure at hospitals/clinics taking care of T1D patients in these regions. Perhaps the improved communication with physicians in patients from the central region (which includes Riyadh, the Capital) is not surprising since it has the most advanced medical system among the regions of the Kingdom; so, it's plausible that hospitals in the central region are more ready to adopt telecommunication with patients. This all comes down to the centralized healthcare system in KSA where main cities receive more healthcare focus; Al Kabba et al. pointed out that Saudi patients in many peripheral areas have to travel to one of the main cities to seek healthcare [10]. As this situation may reoccur, it is highly important that healthcare providers in other regions of the Kingdom prepare their work setting to be able to adopt telecommunication with patients whenever needed. In a recent study in KSA, patients with diabetes agreed that telemedicine is an essential service. The population of this study came from a tertiary center in Riyadh and many of the patients were relatives to university staff, thus had high level of education [11]. Level of education and geographical region were both predictors for reporting communication with the physician in our study. It is worth exploring the reasons behind which patients less than 14 and more than 40 years of age, and those without a University degree; were all less likely to have communicated with their physicians.

In our survey, no statistically significant differences were noted in the occurrence of severe hypoglycemia or DKA between those who communicated with their physicians during the pandemic period compared to those who did not communicate. However, there is evidence that remote communication with people with diabetes using text-messages (either automated or those with inputs from healthcare providers) can result in a significant improvement in glycemic control of T1D [12]. Further research on the role of telemedicine in its multiple forms (such as telephone calls, two-way video calls, interactive voice response calls, and email) in the management of T1D in KSA is required.

We developed the survey's questions to be direct, and easy to understand and answer. The value of our study is strengthened by the large number of respondents from all over the Saudi Kingdom. To our knowledge, this is the largest study of its kind to determine the effects of lockdown among T1D patients in Saudi Arabia. However, findings of the present study should be interpreted with caution given some limitations. The study was conducted early during curfew period, thus results of DKA and hypoglycemia rates may

not reflect the true effect of the curfew as it would have if conducted by the end of the curfew. Additionally, given the nature of online surveys, the accuracy of respondents' answers cannot be verified (we relied on patients' self-report of DKA and hypoglycemia); and the absence of a trained interviewer to clarify responses could have led to less reliable data. Since the survey was distributed by healthcare workers via WhatsApp to T1D patients under their care, there is risk for selection bias to patients whose response could reflect these healthcare workers in a favorable way and to patients who were active users of WhatsApp during the study period. Selection bias could have also been introduced due to the aptitude of the younger generation and individuals with graduate/postgraduate with technology and smartphones.

5. Conclusions

We found that patients with T1D reported difficulties with securing necessary medications and/or supplies related to their disease management and that maintaining communication with the treating physician was important during the lockdown period. As the world is still going through the COVID-19 pandemic, we urge healthcare officials in KSA to address obstacles facing patients with T1D in getting their insulin and necessary supplies; as well as address vulnerable patients particularly the younger age group, those living outside the central region, and those with low monthly income. This will result in more efficient management of the disease and will eventually enhance glycemic control and minimize the rate of diabetic complications especially during any upcoming lockdown.

Conflict of interest

The authors declare that there are no conflicts of interest. The authors received no funding from an external source.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.pcd.2021.07.005>.

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